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Acetyl Chloride−Silver Nitrate−Acetonitrile: A Reagent System for the Synthesis of 2-Nitroglycals and 2-Nitro-1-Acetamido Sugars from Glycals

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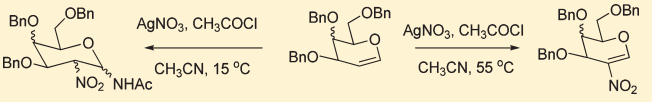
Supporting Information

ABSTRACT: A new reagent system comprising acetyl chloride, silver nitrate, and acetonitrile has been developed for the synthesis of 2-nitroglycals from the corresponding glycals. Under certain conditions, the formation of 2-nitro-1-acetamido sugars has also been observed. In addition, a few other non-carbohydrate-derived olefins also gave the corrresponding conjugated nitroolefins.



Nitroalkenes are of great importance in organic synthesis[1] because of their ability to behave as excellent Michael acceptors,[1,2] as dienophiles,[3] and even as dienes[4] in (4 + 2) cycloadditions leading to useful synthons carrying a nitro functionality. The nitro group containing compounds are also of enormous importance as the nitro group could be easily trnsformed into a variety of other functionalities.[1,5] Thus, for example, a primary or a secondary nitro group can be converted to a carbonyl group via the well-known Nef reaction.[6] The nitro group can also be converted to amines by reduction and also into the corresponding oximes, hydroxyl amines, and nitroso compounds.[7] The nitro group, and especially the tertiary nitro group, is also susceptible to both inter- and intramolecular C−C bond formation in the presence of n-Bu_3SnH via radical pathways.[8,9] Conjugated nitroalkenes are also good substrates for asymmetric Michael reactions[10] owing to the binding capability of the nitro group with the catalysts.

In the domain of carbohydrate chemistry, 2-nitroglycals have gained attention in recent years as versatile synthetic intermediates for the synthesis of various *O*-, *C*-, and *N*-glycosides because they permit easy conjugate addition of a variety of nucleophiles at the anomeric center.[11,12] The 2-nitro glycosides, in turn, are valuable precursors for the synthesis of biologically important 2-deoxy-2-amino glycosides which are constituents of various nucleoside and aminoglycosidic antibiotics.[13] In addition, many other biologically important monocyclic and bicyclic molecules have been procured from 2-nitro glycosides and 2-nitroglycals. More recently, we have also shown the utility of 2-nitroglycals in the synthesis of 2-*C*-branched *O*-galactosides and related compounds.[9]

Although the nitration of aromatic compounds is extensively studied,[14] not many reports are available in the literature for the conversion of olefins to conjugated nitroolefins.[15] Moreover, only two methods are available for the synthesis of 2-nitroglycals from glycals, one of which requires the combination of concentrated nitric acid and acetic anhydride.[11] This method, although useful, is a two-step process which involves tedious workup besides performing the reactions at low temperatures (∼ −35 °C). The other method using nitronium tetrafluoroborate[16] is also carried out at low temperature (−40 °C) involving a two-step process. Thus, there is a need for the development of a new, experimentally simple, and efficient method for the nitration of glycals that works under neutral conditions.

We have been interested in the chemistry of aliphatic nitro compounds for a long time[17] and also have been involved in the functionalization of glycals[18,19] toward the synthesis of biologically important molecules. At the same time, we also have been interested in developing a new method for the synthesis of 2-nitro-1-amino sugars which could be useful substrates for the synthesis of biologically significant 2-amino-β-glycosylamines that form the core in *N*-linked glycoproteins and glycopeptides,[20] molecules that play a crucial role in cell recognition and signal transduction.

In light of the fact that *N*-acetamido groups of the natural glycopeptides (GlcNAc-β-GlcNAc-β-) introduce a unique conformational effect into the interglycosidic and glycopeptide linkages,[21] synthesis of 1,2-differentially protected amines[22] could be of great significance. 2-Nitro-1-amino sugars can also act as precursors for the synthesis of 2-deoxy-1-amino sugar derivatives. Recently, we introduced a new reagent system comprising oxalyl chloride−$AgNO_3$−CH_3CN for the vicinal-chloroacetamidation of olefins.[19] This reagent system was anticipated to be the source of the nitronium ion but was proven to be the source of the chloronium ion as shown in Scheme 1, resulting in the vicinal-chloroacetamidation of olefins. With the same idea of producing a nitronium ion source, we presumed that a new and somewhat similar reagent system acetyl chloride−$AgNO_3$−CH_3CN would introduce the nitro group providing the expected vicinal nitroacetamide. Thus, we discovered the combination of acetyl chloride and

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Scheme 1. Tentative Mechanism for the Formation of Nitroolefins and Nitroacetamide

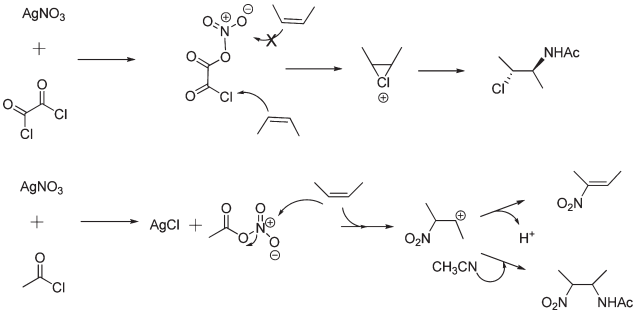
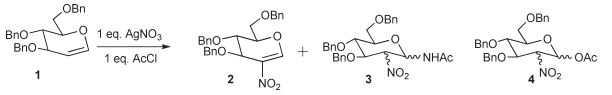


Table 1. Reaction of Tri-O-benzylated Glucal with $AgNO_3$ and Acetyl Chloride in CH_3CN

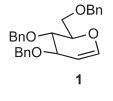
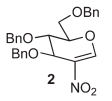
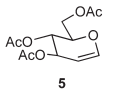
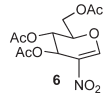
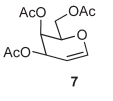
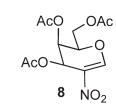
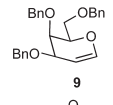
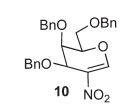
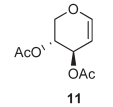
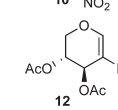
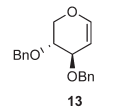
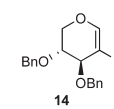
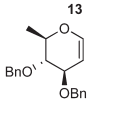
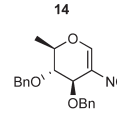
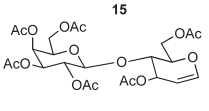
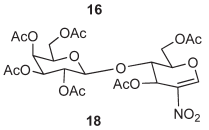
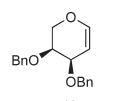
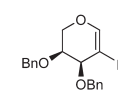


entry no.	acetonitrile	temp.	time	ratio **2**/**3**/**4**	% yield
1	0.5 mL	35 °C	0.5 h	0:1:2.4	82
2	3 mL	15 °C	6 h	1.3:1:0	68
3	3 mL	55 °C	1 h	8:1:0	75
4	7 mL	15 °C	12 h	0:1:0	72
5	7 mL	55 °C	2 h	1:3.1:0	79

silver nitrate, a new source of acetyl nitrate which behaves as an excellent source of nitronium ion.

In our initial experiments, 0.24 mmol of tri-*O*-benzylated glucal **1** was treated with 1 equiv of silver nitrate and 1 equiv of acetyl chloride in 0.5 mL of acetonitrile at 35 °C. We observed the formation of a complex mixture of nitroacetamides **3** (Table 1) and nitroacetates **4** by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. We carried out our study on tri-*O*-benzylated glucal **1** under different temperatures and different dilutions of the reagent in acetonitrile, the results of which are summarized in Table 1. The reaction was observed to be sensitive to both the temperature as well as the dilution. We obtained nitroolefin as a major product under one set of reaction conditions and nitroacetamide under another set of reaction conditions with the same reagent system. Thus, the reaction when performed at 55 °C facilitates the elimination providing 2-nitroglucal as the major product, whereas it gives the vicinal-nitroacetamide without any eliminated product at 15 °C, albeit the reaction takes a long time for completion. However, to our displeasure, formation of a mixture of all four diastereomers of nitroacetamides that are chromatographically inseparable is observed under all the different conditions suggesting that the reaction proceeds through the formaton of an oxonium ion. Besides, the nitronium ion can attack the double bond of the tri-*O*-benzylated glucal **1** from either side since there is no steric demand in this case. Although there is a competitive nucleophilicity between the acetate group and the acetonitrile, the formation of the nitroacetates **4** is observed only under less diluted conditions (entry 1, Table 1), and the possibility of the attack of the acetate ion is diminished by the larger dilution. Therefore, we carried out our study for the conversion of glycals into

Table 2. Nitration of Various Glycals Using the New Reagent System

Entry	Substrate	Product	% Yield
1	 **1**	 **2**	55
2	 **5**	 **6**	94
3	 **7**	 **8**	93
4	 **9**	 **10**	62
5	 **11**	 **12**	82
6	 **13**	 **14**	33
7	 **15**	 **16**	39
8	 **17**	 **18**	74
9	 **19**	 **20**	42

2-nitroglycals and performed the reaction on different benzyls and acetyl-protected glycals, the results of which are summarized in Table 2. All the acetylated glycals (**5**, **7**, **11**, **17**) were converted to the corresponding acetylated 2-nitroglycals (**6**, **8**, **12**, **18**) in very high yields with no nitroacetamide side products. On the other hand, the benzylated glycals (**1**, **9**, **13**, **15**, **19**) showed a somewhat poor conversion to the corresponding 2-nitroglycals (**2**, **10**, **14**, **16**, **20**) and gave an inseparable mixture of vicinal-nitroacetamides as the side products in each case even under heating conditions. The proton α to the nitro group in the intermediate oxonium ion species being more acidic in the case of acetylated glycals facilitates the elimination faster under the heating conditions before the solvent molecule (acetonitrile) attacks. Although acetylated 2-nitroglycals were unstable on silica gel column chromatography,[16] all the reactions on acetylated glycals gave the corresponding 2-nitroglycals in high purity after the workup without the need of chromatograhic purification. The reaction on peracetylated lactal **17** also yielded the corresponding 2-nitrolactal **18** in good yield without affecting the glycosidic linkage, thus affirming the utility of the reagent system as a mild nitrating agent. We performed the nitration reaction on methyl cinnamate **21** (Table 3), styrene **23**, and *trans*-stilbene **25**

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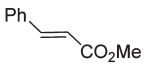
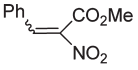
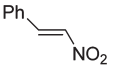
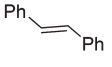
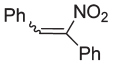
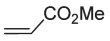
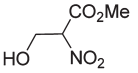
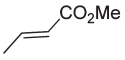
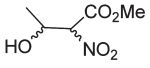
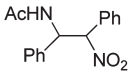
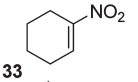
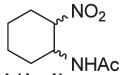
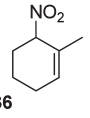
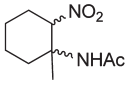
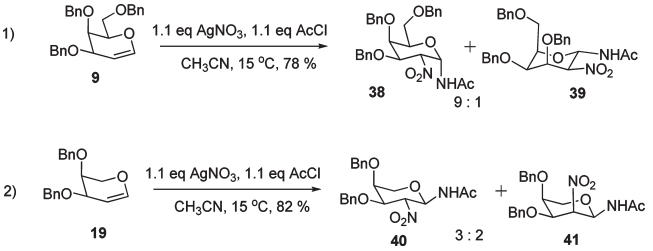
Table 3. Reaction of Non-Carbohydrate Olefins with the New Reagent System

Entry	Substrate	Product	% Yield
1	 **21**	 **22 (1 : 1)**	72
2	 **23**	 **24 (1 : 1)**	55
3	 **25**	 **26 (1 : 1)**	57
4	 **27**	 **28**	51
5	 **29**	 **30 (1 : 0.9)**	73
6	**25**	 **31 (threo isomer)**	66
7	 **32**	 **33** +  **34 (1 : 1)**	33 + 42
8	 **35**	 **36**  **37 (4 : 1)**	48 + 35

to assess the reactivity of the reagent system other than that on enol ethers. It is clear that it works on all activated olefins. The spectral data of all the known compounds were in absolute match with the data reported in the literature.[15,23] Surprisingly, reactions on methyl acrylate **27** as well as methyl crotonate **29** produced the corresponding nitro alcohols as the sole products and did not yield the nitroolefins under the reaction conditions. It is likely that in these cases the β-carbons of the corresponding nitroalkenes, when formed, being highly electrophilic in nature, are trapped by water during workup leading to the nitro alcohols **28** and **30**. The formation of nitroacetamides (cf. entries 6−8, Table 3 and Scheme 2) occurs in a Ritter-type reaction, whereby the carbocation is first trapped by acetonitrile to form the corresponding nitrilium ions which subsequently react with water. Surprisingly, however, in reactions with **27** and **29**, formation of the Ritter type of products was not observed, the reasons for which are not clear at this stage.

Scheme 2. Synthesis of 2-Nitro-1-acetamido Sugars from the Corresponding Glycal



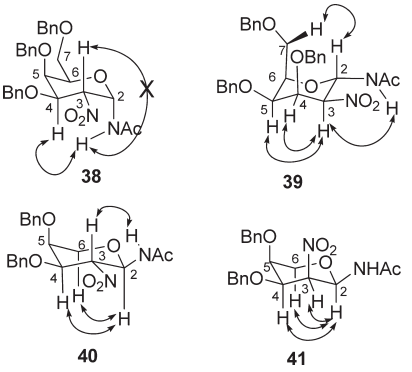


Figure 1. NOE correlation for 2-nitro-1-acetamido sugars.

The reagent has also been tested on simple olefins like cyclohexene **32** and 1-methyl cyclohexene **35**. Cyclohexene, when reacted with the reagent system using general procedure **B** (see Experimental Section), resulted in an inseparable complex mixture of products. However, treating cyclohexene with the reagent system under less diluted conditions, at room temperature, provided a mixture of nitroacetates and vicinal nitroacetamidates which on further treatment with triethylamine gave nitrocyclohexene in 33% yield and a 1:1 mixture of vicinal nitroacetamides **34** in 42% yield, and the data of the compounds are in absolute match with the literature data.[23,24] 1-Methylcyclohexene when treated with the reagent system under the nitration conditions gave the rearranged nitrated product **36** along with an inseparable mixture of a 4:1 mixture of vicinal nitroacetamides **37**. Compound **37** has been confirmed using all the spectral data including DEPT-135 which predicted the presence of a quartenary amine.

To our delight, unlike tri-*O*-benzylated glucal, tri-*O*-benzylated galactal **9** when subjected to the reaction conditions to form the nitroacetamide provided a mixture of chromatographically separable two diastereomers **38** and **39** (Scheme 2) in 9:1 ratio in good yields which could serve as valuable synthons for the synthesis of biologically significant 2-amino-*N*-glycopeptides. The major isomer **38** was confirmed to exist in a $^4C_1$ conformation as analyzed by the NOE experiments (Figure 1). Thus, irradiation of the signal for the −N*H* proton results in the enhancement of the signals for the protons H-4 and H-6, whereas there was no enhancement in the signal for H-3 suggesting that the acetamido group and the nitro group are cis to each other and the acetamido group at the anomeric position is α-oriented. The

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NOE experiments on the minor isomer **39** suggested it to be in $^1C_4$ conformation. Irradiation of the anomeric proton resulted in the enhancement of one of the C-7 protons which is only possible when the compound exists in a $^1C_4$ conformaton, and the acetamido group is equatorially oriented. Besides, irradiation of H-3 resulted in the enhancement of the signals for the protons H-4 and H-5 suggesting the equatorial orientation of the nitro group.

Likewise, di-*O*-benzylated arabinal **19** also gave a mixture of two diastereomeric nitroacetamides **40** and **41** in 3:2 ratio which were chromatographically separable in 82% yield. Irradiation of the signal for H-2 in both the isomers resulted in the enhancement of the corresponding signals for H-4 and H-6 suggesting the $^4C_1$ conformation and the equatorial orientation of −NHAc. Irradiation of the signal for −N*H* in the major isomer **40** resulted in the enhancement of the signal for H-3 showing the trans relation of −NHAc with the nitro group, whereas it resulted in no enhancement of H-3 in the minor isomer **41** suggesting the axial orientation of the nitro group. These observations clearly suggest that the reaction proceeds via an oxonium ion intermediate, and the diastereoselectivity can be obtained only on sterically demanding substrates like galactal and arabinal. Stilbene **25** was also subjected to the same conditions to obtain the threo isomer of the corresponding nitroacetamide **31**[24] in 66% yield. Studies are under progress for the development of improved conditions to obtain the 2-nitro-1-acetamido sugars with this new reagent system and will be published in due course.

In summary, we have developed a new reagent system for the conversion of olefins to nitroolefins. It is an excellent method for the conversion of acetylated glucals to their 2-nitroglucals than their benzyl-protected counterparts. Further, a new method has been developed for the conversion of benzylated glycals to the corresponding 2-nitro-1-acetamido sugars for the first time in good yields which can serve as precursors for the synthesis of 2-amino *N*-glycopeptides.

EXPERIMENTAL SECTION

General Experimental Methods. IR spectra were recorded with FT-IR as a thin film and are expressed in cm^{-1}. ^1H (400 or 500 MHz) and ^{13}C (100 or 125 MHz) NMR spectra were recorded using $CDCl_3$ and sometimes D_2O as a solvent. The stereochemistry of the compounds is assigned with the help of NOE experiments. Chemical shifts are reported in parts per million downfield to tetramethylsilane. Coupling constants are reported and expressed in Hz; splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), and m (multiplet). Optical rotations were measured using a polarimeter at 28 °C. All reactions were carried out using freshly distilled and dry solvents. The visualization of spots on TLC plates was effected by exposure to iodine or spraying with 10% H_2SO_4 and charring. Column chromatography was performed over silica gel (100−200 Mesh) using hexane and ethyl acetate as eluent. Mass spectra were obtained on a high-resolution ESI mass spectrometer.

(A). General Procedure for the Synthesis of 2-Nitroglycals. To a stirred solution of a glycal (0.25 mmol) and $AgNO_3$ (42 mg, 0.25 mmol) in acetonitrile (3.0 mL, 57.5 mmol) at 0 °C was added dropwise acetyl chloride (19.0 μL, 0.25 mmol). After the completion of the addition, the reaction vessel was transferred to an oil bath maintained at 55 °C, and the reaction mixture was stirred for 1 h. After the consumption of the starting material (TLC monitoring), the reaction mixture was brought to room temperature and was neutralized to pH 7 by the addition of solid sodium bicarbonate by checking the pH regularly. The reaction mixture was filtered off using sintered funnel, and the filtrate was concentrated. It was further diluted with 20 mL of dichloromethane and washed with saturated brine solution. The organic phase was dried with Na_2SO_4 and evaporated to obtain a crude product whose column chromatographic purification led to pure 2-nitroglycal.

(B). General Procedure for the Nitration of Non-Carbohydrate Olefins. To a stirred solution of an olefin (0.25 mmol) and $AgNO_3$ (42 mg, 0.25 mmol) in acetonitrile (3.0 mL, 57.5 mmol) at 0 °C was added dropwise acetyl chloride (19.0 μL, 0.25 mmol). After the completion of the addition, the reaction vessel was transferred to an oil bath maintained at 65 °C, and the reaction mixture was stirred for 1 h. After the consumption of the starting material (TLC monitoring), the reaction mixture was neutralized to pH 7 by the addition of solid sodium bicarbonate. The reaction mixture was filtered off using sintered funnel, and the filtrate was concentrated which was further diluted with 20 mL of dichloromethane and washed with saturated brine solution. The organic phase was dried with Na_2SO_4 and then evaporated to obtain a crude product which was purified by column chromatography.

(C). Reaction of Cyclohexene for the Preparation of 1-Nitrocyclohexene. To a stirred solution of an olefin (3.65 mmol) and $AgNO_3$ (613 mg, 3.65 mmol) in acetonitrile (1.0 mL, 18.9 mmol) at 0 °C was added dropwise acetyl chloride (281.0 μL, 3.65 mmol). After the completion of the addition, the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then neutralized to pH 7 by the addition of solid sodium bicarbonate. The reaction mixture was filtered off using a sintered funnel, and the filtrate was concentrated which was further diluted with 20 mL of dichloromethane and washed with saturated brine solution. The organic phase was dried with Na_2SO_4 and then evaporated to obtain a crude product which was treated with triethylamine for another 24 h. The reaction mixture was diluted with 20 mL of dichloromethane, washed with 3 N HCL, followed by saturated brine solution. The organic phase was dried with Na_2SO_4 and then evaporated. The crude product was purified by column chromatography which provided the 1-nitrocyclohexene **33** and the mixture of vicinal nitroacetamides **34** in 32% and 42% yields, respectively.

(D). Procedure for the Synthesis of Nitroacetamides. To a stirred solution of a glycal (0.25 mmol) and $AgNO_3$ (42 mg, 0.25 mmol) in acetonitrile (7.0 mL, 134.1 mmol) at 15 °C was added dropwise acetyl chloride (19 μL, 0.25 mmol). The reaction mixture was stirred for 12 h at the same temperature, and after the consumption of the starting material (TLC consumption), the reaction mixture was neutralized to pH 7 by the addition of a saturated sodium bicarbonate solution. The reaction mixture was filtered off using a sintered funnel, and the filtrate was concentrated, which was further diluted with 20 mL of dichloromethane and washed with saturated brine solution. The organic phase was dried with Na_2SO_4 and then evaporated. The crude product was purified by column chromatography which provided the pure product.

*(3R,4R)-5-Nitro-3,4-dihydro-2H-pyran-3,4-diyl Diacetate (**12**).* Yield: 82%. R_f: 0.45 (hexane:ethyl acetate, 7:3), $[\alpha]_D^{28} = +77.2$ (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 2926, 2854, 1751, 1642, 1510, 1371, 1222, 1045 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 5.98 (s, 1H), 5.10 (s, 1H), 4.53 (d, J = 12.6 Hz, 1H), 4.04 (d, J = 12.9 Hz, 1H), 2.08 (brs, 6H, 2-OCOC*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 168.8, 157.3, 128.3, 65.5, 64.8, 60.8, 20.6(2). HRMS calcd for $C_9H_{12}NO_7$ $[M + H]^+$ 246.0614. Found: 246.0617.

*(3R,4R)-3,4-Bis(benzyloxy)-5-nitro-3,4-dihydro-2H-pyran (**14**).* Yield: 33%. R_f: 0.45 (hexane:ethyl acetate, 4:1), $[\alpha]_D^{28} = -27.7$ (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 3070, 2921, 1686, 1637, 1499, 1292, 1240, 1128, 1072, 935, 707 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.35−7.23 (m, 10H, Ar−H), 4.74−4.70 (m, 2H), 4.65 (d, J = 11.0 Hz, 1H), 4.49 (m, 2H), 4.37 (dt, J = 1.8 Hz, J = 10.1 Hz, 1H), 4.06 (d, J = 11.9 Hz, 1H), 3.70 (d, J = 2.7 Hz, 1H. ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 137.3, 136.7, 131.1, 128.6−127.7 (m, Ar−C), 72.7, 71.3, 70.1, 66.6, 65.8. HRMS calcd for $C_{19}H_{19}NO_5Na$ $[M + Na]^+$ 364.1161. Found: 364.1165.

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*(2R,3R,4R)-3,4-Bis(benzyloxy)-2-methyl-5-nitro-3,4-dihydro-2H-pyran (**16**).* Yield: 39%. R_f: 0.60 (hexane:ethyl acetate, 9:1), $[\alpha]_D^{28}$ = +86.0 (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 3031, 2918, 1638, 1498, 1342, 1208, 1073, 1027, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.34−7.21 (m, 10H, Ar−H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.71 (t, *J* = 2.2 Hz, 1H), 4.64−4.61 (m, 2H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 3.64 (d, *J* = 1.9 Hz, 1H), 1.41 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5, 137.6, 136.8, 134.5, 128.8−127.6 (m, Ar−C), 76.0, 74.3, 73.0, 71.6, 68.2, 16.01. HRMS calcd for $C_{20}H_{21}NO_5Na$ $[M + Na]^+$ 378.1268. Found: 378.1267.

*(2S,3R,4S,5S,6R)-2-((2R,3S,4S)-4-Acetoxy-2-(acetoxymethyl)-5-nitro-3,4-dihydro-2H-pyran-3-yloxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl Triacetate (**18**).* Yield: 74%. R_f: 0.45 (hexane:ethyl acetate, 1:4), $[\alpha]_D^{28}$ = −54.4 (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 2927, 2856, 1749, 1640, 1508, 1365, 1220, 1042 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 6.30 (s, 1H), 5.36 (d, *J* = 3.1 Hz, 1H), 5.11 (s, 1H), 5.01 (d, *J* = 3.4 Hz, *J* = 10.6 Hz, 1H), 4.73 (d, *J* = 7.7 Hz, 1H), 4.58 (m, 1H), 4.29 (d, *J* = 8.6 Hz, *J* = 12.3 Hz, 1H), 4.16−4.07 (m, 4H), 4.02 (t, *J* = 6.3 Hz, 1H), 2.13 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.3, 170.2, 170.1, 169.5, 169.2, 155.0, 127.5, 102.0, 73.3, 71.4, 70.7, 68.8, 66.9, 61.9, 61.3, 60.6. HRMS calcd for $C_{24}H_{31}NO_{17}Na$ $[M + Na]^+$ 628.1490. Found: 628.1494.

*(3S,4R)-3,4-Bis(benzyloxy)-5-nitro-3,4-dihydro-2H-pyran (**20**).* Yield: 42%. R_f: 0.52 (hexane:ethyl acetate, 9:1), $[\alpha]_D^{28}$ = −69.9 (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 3032, 2915, 1636, 1498, 1340, 1210, 1070, 1028, 739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.38−7.25 (m, 10H, Ar−H), 4.99 (d, *J* = 2.15 Hz, 1H), 4.93 (d, *J* = 10.7 Hz, 1H), 4.81 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.21−4.17 (m, 2H), 3.78 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 138.0, 137.1, 131.9, 128.8−127.7 (m, Ar−C), 74.6, 72.3, 71.8, 67.2, 64.3. HRMS calcd for $C_{19}H_{19}NO_5Na$ $[M + Na]^+$ 364.1161. Found: 364.1164.

*Methyl 3-Hydroxy-2-nitropropanoate (**28**).* Yield: 51%. R_f: 0.45 (hexane:ethyl acetate, 4:1). IR (neat) ν_{max}: 3472, 2960, 2925, 1748, 1560, 1441,1420, 1227, 1126 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.75 (dd, *J* = 2.6 Hz, *J* = 3.8 Hz, 2H), 4.65 (t, *J* = 4.2 Hz, 1H), 3.85 (s, 3H), 3.55 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 77.3, 67.6, 53. HRMS calcd for $C_4H_7NO_5$ $[M]^+$ 149.0324. Found: 149.0323.

*Methyl 3-Hydroxy-2-nitrobutanoate (**30**).* Yield: 73%. R_f: 0.55 (hexane:ethyl acetate, 4:1). IR (neat) ν_{max}: 3475, 2968, 2928, 1749, 1559, 1438, 1422, 1227, 1125 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) diastereomeric mixture, 1.4:1: δ 4.92 (m, 1H, major diastereomer), 4.86 (brs, 1H, minor diastereomer), 4.82 (m, 1H, minor diastereomer), 4.35 (brs, 1H, major diastereomer), 3.85 (s, 6H, both diastereomers, $-OCH_3$), 3.32 (brs, 2H, both diastereomers). ^{13}C NMR (125 MHz, $CDCl_3$), both diastereomers: δ 171.6, 171.3, 83.4, 83.1, 71.9, 71.5, 53.6, 53.5, 15.1, 12.6. HRMS calcd for $C_5H_9NO_5Na$ $[M + Na]^+$ 186.0378. Found: 186.0379.

*1-Methyl-6-nitrocyclohex-1-ene (**36**).* Yield: 48%. R_f: 0.85 (hexane: ethyl acetate, 99:1). IR (neat) ν_{max}: 2946, 2866, 1639, 1549, 1333, 1278, 822 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (brs, 1H), 4.88 (brs, 1H), 2.29−2.32 (m, 2H), 2.03−2.16 (m, 2H), 1.73 (s, 3H), 1.59−1.69 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.2, 126.5, 85.8, 28.5, 24.7, 20.9, 17.8. HRMS calcd for $C_7H_{12}NO_2$ $[M + Ha]^+$ 142.0868. Found: 142.0869.

DEPT-135 Positive peaks: δ 131.2, 85.8, 20.9. Negative peaks: δ 28.5, 14.7, 17.8.

*N-(1-Methyl-2-nitrocyclohexyl)acetamide (**37**).* Yield: 73%. R_f: 0.55 (hexane:ethyl acetate, 4:1). IR (neat) ν_{max}: 2947, 2868, 1657, 1547, 1278, 821 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) diastereomeric mixture, 4:1: δ 6.24 (brs, 1H, $-NH$, minor diastereomer), 5.80 (brs, 1H, $-NH$, major diastereomer), 5.56 (dd, *J* = 5.1 Hz, *J* = 11.1 Hz, 1H, major diastereomer), 4.49 (brd, *J* = 14.8 Hz, 1H, minor diastereomer), 2.97 (m, 1H, minor diastereomer), 2.52 (td, *J* = 4.0 Hz, *J* = 12.8 Hz, 1H, major diastereomer), 2.02−1.97 (m, 2H, both diastereomers), 1.94 (s, 3H, $-NHCOCH_3$, minor diastereomer), 1.91 (s, 3H, -$NHCOCH_3$, major diastereomer), 1.82−1.59 (m, 6H, both diastereomers), 1.40 (s, 3H, $-CH_3$, minor diastereomer), 1.35 (m, 4H, both diastereomers), 1.20 (s, 3H, $-CH_3$, major diastereomer). ^{13}C NMR (125 MHz, $CDCl_3$), both diastereomers: δ 170.6, 170.0, 92.4, 86.1, 56.4, 55.1, 35.4, 33.5, 26.9, 26.7, 24.5, 23.6, 23.3, 21.8, 21.8, 20.4, 19.9, 19.9. HRMS calcd for $C_9H_{17}N_2O_3$ $[M + H]^+$ 201.1241. Found: 201.1244.

DEPT-135 Positive peaks: δ 92.4, 86.1, 24.5, 23.6, 19.6, 19.6. Negative peaks: δ 35.4, 33.6, 26.9, 26.7, 23.3, 21.8, 21.8, 20.4.

*N-((2S,3R,4R,5R,6R)-4,5-Bis(benzyloxy)-6-(benzyloxy methyl)-3-nitrotetrahydro-2H-pyran-2-yl)acetamide (**38**).* Yield: 70%. R_f: 0.50 (hexane:ethyl acetate, 3:2), $[\alpha]_D^{28}$ = +24.6 (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 3293, 3061, 3032, 2922, 2869, 1663, 1552, 1374, 1273, 1096, 1064, 738, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34−7.23 (m, 15H, Ar−H), 6.73 (d, *J* = 8.4 Hz, 1H, $-NH$), 6.14 (dd, *J* = 5.8 Hz, *J* = 8.6 Hz, 1H, H-2), 5.30 (dd, *J* = 5.5 Hz, *J* = 11.0 Hz, 1H, H-3), 4.82 (d, *J* = 11.3 Hz, 1H, $-OCHPh$), 4.71 (d, *J* = 11.0 Hz, 1H, $-OCHPh$), 4.59 (d, *J* = 11.0 Hz, 1H, $-OCHPh$), 4.51 (d, *J* = 11.0 Hz, 1H, $-OCHPh$), 4.46 (d, *J* = 11.6 Hz, 1H, $-OCHPh$), 4.40 (d, *J* = 11.6 Hz, 1H, $-OCHPh$), 4.30 (brd, *J* = 11.1 Hz, 1H, H-4), 4.13 (s, 1H, H-5), 3.89 (t, *J* = 7.3 Hz, 1H, H-6), 3.60 (t, *J* = 8.5 Hz, 1H, H-7), 3.51 (dd, *J* = 5.2 Hz, *J* = 8.8 Hz, 1H, H-7′), 1.97 (s, 3H, $-NHCOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 137.8, 137.6, 136.7, 128.6−128.0 (m, Ar−C), 83.8, 75.7, 75.1, 74.1, 73.7, 72.6, 72.5, 70.6, 67.7, 23.4. HRMS calcd for $C_{29}H_{33}N_2O_7$ $[M + H]^+$ 521.2288. Found: 521.2283.

*N-((2S,3S,4R,5R,6R)-4,5-Bis(benzyloxy)-6-(benzyloxy methyl)-3-nitrotetrahydro-2H-pyran-2-yl)acetamide (**39**).* Yield: 8%. R_f: 0.52 (hexane:ethyl acetate, 3:2), $[\alpha]_D^{28}$ = +45.0 (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 3296, 3063, 3031, 2923, 2870, 1672, 1554, 1372, 1091, 1027, 738, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35−7.13 (m, 15H, Ar−H), 6.73 (brd, *J* = 8.5 Hz, 1H, $-NH$), 5.87 (t, *J* = 9.1 Hz, 1H, H-2), 4.80 (dd, *J* = 3.3 Hz, *J* = 9.4 Hz, 1H, H-3), 4.72 (d, *J* = 11.0 Hz, 1H, $-OCHPh$), 4.63 (d, *J* = 12.2 Hz, 1H, $-OCHPh$), 4.56 (m, 3H, H-4, 2-$OCHPh$), 4.48 (m, 3H, 3-$OCHPh$), 4.34 (t, *J* = 6.7 Hz, 1H, H-6), 4.17 (dd, *J* = 9.1 Hz, *J* = 12.2 Hz, 1H, H-7), 3.78 (m, 2H, H-7′, H-5), 1.97 (s, 3H, -$NHCOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 138.2, 137.2, 136.9, 128.7−127.6 (m, Ar−C), 82.5, 75.6, 75.4, 75.1, 73.6, 72.0, 69.8, 65.7, 23.6. HRMS calcd for $C_{29}H_{33}N_2O_7$ $[M + H]^+$ 521.2288. Found: 521.2287.

*N-((2R,3R,4R,5S)-4,5-Bis(benzyloxy)-3-nitrotetrahydro-2H-pyran-2-yl)acetamide (**40**).* Yield: 59%. R_f: 0.35 (hexane:ethyl acetate, 4:1), $[\alpha]_D^{28}$ = +66.3 (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 3292, 3064, 3029, 2920, 2870, 1670, 1550, 1369, 1095, 1063, 739, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.41 (m, 10H, Ar−H), 6.61 (d, *J* = 8.5 Hz, 1H, $-NH$), 5.24 (t, *J* = 8.0 Hz, 1H, H-2), 4.72−4.58 (m, 4H), 4.10 (t, *J* = 8.2 Hz, 1H, H-3), 3.96 (dd, *J* = 3.8 Hz, *J* = 12.6 Hz, 1H, H-6), 3.79 (s, 1H, H-5), 3.65 (dd, *J* = 2.9 Hz, *J* = 8.8 Hz, 1H, H-4), 3.54 (dd, *J* = 1.6 Hz, *J* = 12.6 Hz, 1H, H-6′), 1.98(s, 3H, $-NHCOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 137.6, 137.2, 128.5−127.4 (m, Ar−C), 80.5, 79.7, 72.9, 71.8, 71.6, 64.3, 58.3, 29.6, 29.3, 23.2 calcd for $C_{21}H_{25}N_2O_6$ $[M + H]^+$ 401.1713. Found: 401.1716.

*N-((2R,3S,4R,5S)-4,5-Bis(benzyloxy)-3-nitrotetrahydro-2H-pyran-2-yl)acetamide (**41**).* Yield: 23%. R_f: 0.38 (hexane:ethyl acetate, 4:1), $[\alpha]_D^{28}$ = −36.7 (*c* 0.25, CH_2Cl_2). IR (neat) ν_{max}: 3064, 3029, 2920, 2870, 1670, 1550, 1369, 1095, 1063, 739, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34−7.25 (m, 10H, Ar−H), 6.20 (d, *J* = 9.5 Hz, 1H, $-NH$), 5.77 (d, *J* = 9.7 Hz, 1H, H-2), 4.78 (d, *J* = 11.9 Hz, 1H, $-OCHPh$), 4.69 (d, *J* = 11.9 Hz, 1H, $-OCHPh$), 4.52 (s, 2H, $-OCH_2Ph$), 4.07 (brs, 1 H), 4.02 (m, 2H), 3.96 (t, *J* = 10.4 Hz, 1H, H-6), 3.83 (dd, *J* = 3.0 Hz, *J* = 10.7 Hz, 1H, H-7), 2.01 (s, 3H, $-NHCOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 137.7, 137.5, 128.4−127.5 (m, Ar−C), 75.7, 73.7, 73.3, 71.6, 70.4, 64.0, 59.3, 29.6, 23.3. HRMS calcd for $C_{21}H_{25}N_2O_6$ $[M + H]^+$ 401.1713. Found: 401.1718.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H NMR and ^{13}C NMR spectra of all the new compounds, DEPT-135 spectra of compounds **36** and **37**, COSY and NOE spectra of compounds **38**, **39**, **40**, and **41**, and Homo nuclear decoupled spectra of the compounds **40** and **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Feuer, H.; Nielsen, A. T. *Nitro Compounds*; VCH Publishers, Inc.: New York, 1990. (c) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751.

(2) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamomn Press: Oxford, 1992. (b) Ballini, R.; Maggi, R.; Palmieri, A.; Sartori, G. *Synthesis* **2007**, 3017.

(3) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pegamon Press: Oxford, 1990. (b) Kim, W. H.; Lee, J. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12576.

(4) (a) Denmark, S. E.; Baiazitov, R. Y.; Nguyan, S. T. *Tetrahedron* **2009**, *65*, 6535.

(5) (a) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (b) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423.

(6) (a) Krawczyk, H.; Albrecht, L.; Wojciechowski, J.; Wolf, W. M. *Tetrahedron* **2006**, *62*, 9135. (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; p 603. (c) Pinnick, H. W. *Org. React.* **1990**, *38*, 655. (d) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.

(7) (a) Seebach, D.; Beck, A. K.; Lehr, F.; Weller, T.; Colvin, E. *Angew. Chem., Int. Ed.* **1981**, *20*, 397. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; John Wiley and Sons, Inc.: New York, 1999.

(8) (a) Ono, N.; Kaji, A. *Synthesis* **1986**, 693. (b) Bowman, W. R.; Crosby, D.; Westlake, P. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 73.

(9) Kancharla, P. K.; Vankar, Y. D. *J. Org. Chem.* **2010**, *75*, 8457.

(10) (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (b) Lykke, L.; Monge, D.; Nielsen, M.; Jorgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 13330.

(11) (a) Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1609. (b) Schmidt, R. R.; Vankar, Y. D. *Acc. Chem. Res.* **2008**, *41*, 1059.

(12) (a) Xue, W.; Sun, J.; Yu, B. *J. Org. Chem.* **2009**, *74*, 5079. (b) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900. (c) Reddy, B. G.; Vankar, Y. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2001.

(13) Haddad, J.; Kotra, L.; Mobashery, S. Aminoglycoside Antibiotics: Structures and Mechanisms of Action. In *Glycochemistry Principles, Synthesis and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Marcel Dekker: New York, 2001; p 307.

(14) (a) Koley, D.; Colon, O. C.; Savinov, S. N. *Org. Lett.* **2009**, *11*, 4172. (b) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898 and references cited therein. (c) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH: New York, 1989. (d) Surya Prakash, G. K.; Mathew, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1726.

(15) (a) Jovel, I.; Prateeptongkum, S.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2493. (b) Stepanov, A. V.; Veselovsky, V. V. *Russ. Chem. Rev.* **2003**, *72*, 327. (c) Tanaka, M.; Muro, E.; Ando, H.; Xu, Q.; Fujiwara, M.; Souma, Y.; Yamaguchi, Y. *J. Org. Chem.* **2000**, *65*, 2972.

(16) Holzapfel, C. W.; Marais, C. F.; Van Dyk, M. S. *Synth. Commun.* **1988**, *18*, 97.

(17) (a) Gupta, A.; Haque, A.; Vankar, Y. D. *J. Chem. Soc., Chem. Commun.* **1996**, 1653. (b) Jayakanthan, K.; Madhusudanan, K. P.; Vankar, Y. D. *Tetrahedron* **2004**, *60*, 397. (c) Jayakanthan, K.; Vankar, Y. D. *Org. Lett.* **2005**, *7*, 5441.

(18) (a) Rawal, G. K.; Rani, S.; Madhusudanan, K. P.; Vankar, Y. D. *Synthesis* **2007**, 294. (b) Agarwal, A.; Rani, S.; Vankar, Y. D. *J. Org. Chem.* **2004**, *69*, 6137. (c) Reddy, B. G.; Madhusudanan, K. P.; Vankar, Y. D. *J. Org. Chem.* **2004**, *69*, 2630. (d) Pachamuthu, K.; Vankar, Y. D. *J. Org. Chem.* **2001**, *66*, 7511.

(19) Rawal, G. K.; Kumar, A.; Tawar, U.; Vankar, Y. D. *Org. Lett.* **2007**, *9*, 5171.

(20) (a) Liu, L.; Bannett, C. S.; Wong, C.-H. *Chem. Commun.* **2006**, 21. (b) Kaneshiro, C. M.; Michael, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 1077.

(21) Bosques, C. J.; Tschampel, S. M.; Woods, R. J.; Impariali, B. *J. Am. Chem. Soc.* **2004**, *126*, 8421.

(22) Kumar, V.; Ramesh, N. G. *Chem. Commun.* **2006**, 4952.

(23) (a) Lemieux, R. U.; Nagabushan, T. L.; O'Neill, I. K. *Tetrahedron Lett.* **1964**, *5*, 1909. (b) Blanco-Ania, D.; Hermkens, P. H. H.; Sliedregt, L. A. J. M.; Scheeren, H. W. *Tetrahedron* **2009**, *65*, 5393. (c) Poe, S. L.; Kobaslija, M.; Maquade, D. T. *J. Am. Chem. Soc.* **2006**, *128*, 15586. (d) Milner, S. E.; Brossat, M.; Moody, T. S.; Elcoate, T. S.; Lawrence, S. E.; Maguire, A. R. *Tetrahedron: Asymmetry* **2010**, *21*, 1011.

(24) Bloom, A. J.; Fleischmann, M.; Mellor, J. M. *J. Chem. Soc., Perkin Trans.* **1984**, 2357.